Remarks

This amendment is responsive to the Office Action dated October 10, 2007 in which it was stated that, due to the Office's rejection of the term "derivative" in the co-pending application 10/1682584, the Examiner has chosen to reject the instant claims on the same basis.

New claims 31-52 are filed herewith, taking into consideration the Office Action dated October 10, 2007. Facts and explanations are presented below showing patentability of the presently claimed subject matter.

Following the October 10, 2007 Office Action, a telephone interview was held with Examiner Frederick Krass on December 6, 2007 to discuss the basis of the current rejection. Agreement was not reached. The Examiner suggested that additional claims be presented for consideration. Three claim groups were proposed by the Examiner and are listed in the Examiner's Interview Summary Record mailed 12/12/2007. The Examiner's suggestions have been included in formulating the claims presented herein. However, in consideration of the possibility of a need for an appeal on a portion of the suggested claims, the applicant has elected also present further claims not specifically discussed at the interview.

Claims 1, 8, 9, 11, 27 and 28, previously presented and not amended herein, correspond to the Examiner's suggested claim group 3). Further consideration is requested in view of the arguments presented below.

I. Written Description Rejection

Claims 1, 8, 9, 11, 27 and 28 have been rejected under 35 U.S.C. § 112, first paragraph, asserting that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time of the filing of application, had possession of the claimed invention. Applicant does not agree.

As detailed below, the specification of the present application does contain written description of the claimed subject matter satisfying the requirements of 35 U.S.C. § 112, as construed in the cited case *Univ of Rochester v GD Searle,* 69 USPQ2d 1886 (Fed. Cir. 2004).

In making the Written Description Rejection, the Office Action states that the specification fails to provide adequate written description for the compounds that can be used in place of cyclopamine to carry out the invention. The rationale for the rejection is purported to be derived from a quotation from *Rochester* (at 69 USPQ2d 1892), which the Office Action argues creates a rule that purely functional descriptions are "generally insufficient" to meet the written description requirement. The *Rochester* quotation is misleadingly incomplete, as it omits the critical sentence:

> The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described.

Thus, compliance with the written description requirement is essentially a fact-based inquiry that will necessarily vary depending on the nature of the invention claimed.

It has never been the law that an already described class of compounds, known to have properties in common, cannot be claimed by recitation of those shared properties. Indeed the *Rochester* decision makes it very clear that it was the specific state of the art (a lack of *any* known members of the class), not the use of functional language *per se*, that caused the finding of inadequate written description. Specifically, the *Rochester* court states:

> [I]t is undisputed that the '850 patent does not disclose any compounds that can be used in its claimed methods. The claimed methods thus cannot be practiced based on the patent's specification, even considering the knowledge of one skilled in the art. ***No compounds that will perform the claimed method are disclosed, nor has any evidence been shown that such a compound was known.***
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> 69 USPQ2d 1895 (emphasis added)

The court went further to distinguish this state of the art from that in *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 54 USPQ2d 1227 (Fed. Cir. 2000) ("*Unocal*").

> Third, Rochester's reliance on *Unocal* is unavailing. Although we held in that case that a "***descri[ption] of the exact chemical component of each combination that falls within the range claims of the ... patent" is not necessary to comply with §112***, we explained that the patentee is nonetheless required to provide sufficient description to show one of skill in the art that the inventor possessed the claimed invention at the time of filing. *Unocal,* 208 F.3d at 997. ***Evidence was adduced in that case that artisans skilled in petroleum refining were aware of the properties of raw petroleum sources and knew how to mix streams of such sources to achieve a final product with desired characteristics.*** Accordingly, we held that the written description requirement was satisfied in that case by specifying the ranges of properties of the claimed gasolines,

> reflecting the way that oil refiners actually formulate gasoline, such that one skilled in the art could recognize what was being claimed. Id. at 992. The present case is not analogous. Rochester did not present any evidence that the ordinarily skilled artisan would be able to identify any compound based on its vague functional description as "a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product."
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> 69 USPQ2d 1895-1896 (emphasis added)

In the present case, the application provides an example of a compound that is a specific inhibitor of Hedgehog/Smoothened signaling (cyclopamine), together with proof of efficacy in treating psoriasis. Additionally there is extensive evidence in the record that a skilled person knows how to identify other compounds that are specific inhibitors of Hedgehog/Smoothened signaling. The accompanying declaration of Dr. Sinan Tas, one of the inventors, specifically addresses this issue in detail and provides the supporting documentation.

The skilled person reading the present application understands from the term "derivatives" and/or "specific inhibitor of Hedgehog/Smoothened signaling" that the inventor possessed the claimed invention at the time of filing. As indicated on page 3, lines 16-22 of the application, cyclopamine (11-deoxojervine) and other teratogenic *Veratrum* alkaloids (e.g. jervine) were known in prior art to inhibit Hh/Smo signaling specifically. Besides cyclopamine, various categories and numerous particular examples of non-cyclopamine molecules were well known in prior art to be suitable to specifically inhibit Hedgehog/Smoothened (Hh/Smo) signaling. Structural features of these molecules and their uses for specifically inhibiting Hh/Smo signaling had been described in numerous prior art publications. In addition, as stated on page 17, lines 22-25 of the application, additional such molecules can be synthesized by those skilled in the art.

A compound defined as a compound that specifically inhibits Hh/Smo signaling is understood clearly by a person skilled in art. This functional definition is adequate for him/her to know whether a given compound would fall within or out of the defined category of compounds, particularly since numerous compounds having different structural features had been described in prior art to inhibit Hh/Smo signaling specifically and the methods for assaying Hh/Smo signaling were common knowledge in prior art. The scientific publications cited on page 3, lines 19-22 of specification had shown that cyclopamine or jervine could be used to specifically inhibit Hh/Smo signaling (see Cooper MK et al, *Science* 1998;280:1603-l607, Abstract, "... *these compounds* *specifically block the Sonic hedgehog (Shh) signaling pathway";* Incardona JP et al, *Development* 1998;125:3553-3562, Abstract, "... *cyclopamine-induced teratogenesis is due to a...direct antagonism of Shh signal transduction")*. Thus, inhibition of Hh/Smo signaling specifically was a well-known biological effect of cyclopamine and the specification mentions this fact. Hh family of proteins were discovered originally through their effects on the patterning of embryo where they were found to induce differentiation of various target cells during development and, in fact, cyolopamine and other teratogenic *Veratrum* alkaloids were deduced to inhibit Hh/Smo signaling specifically from the finding that they selectively inhibited the differentiation events induced by a Hh family protein (Shh) in the developing nervous system (Cooper MK et al, *Science* 1998;280:1603-1607; Incardona JP et al, *Development* 1998;125:3553-3562). The same Shh-induced differentiation events inhibited by teratogenic *Veratrum* alkaloids had been shown to be selectively inhibited by affinity purified anti-Shh antibodies as well (Ericson J et al, *Cell* 1996;87:661-673). Signaling by Shh and by other Hh family proteins was shown in prior art to be specifically inhibited also by monoclonal antibodies and by other molecules recognizing Hh proteins (see Ericson J et al, *Cell* 1996;87:661-673; Goodrich LV et al, *Neuron* 1998;21:1243-1257; Chuang PT et at, *Nature* 1999;397:617-621; Wang LC et al, *Journal of Investigative Dermatology* 2000;114:901-908; Treier M et al, *Development* 2001;128:377-386). For example, the scientific publication cited on page 3, lines 22-25 of the specification of the present application refers to the inhibition of Hh/Smo signaling by cyclopamine and describes that non-cyclopamine molecules can also be used to inhibit Hh/Smo signaling similarly (see Goodrich LV et al, *Neuron,* 1998;21:1243-1257). Still other categories of non-cyclopamine molecules had also been described in prior art to specifically inhibit Hh/Smo signaling as demonstrated e.g. by assaying for the effects on Gli family proteins (intranuclear executors of Hh/Smo signaling) (see Williams KP et al, *Journal of Cell Science* 1999;112:4405-4414*)*. At page 17 lines 22-25, this known inhibition is specifically tied to the definition of alternative compounds taught to be usable in the invention.

Methods of assaying Hh/Smo signaling and methods of synthesis of libraries of related molecules (e.g. combinatorial chemistry) were common knowledge in prior art. After reading the present application, a person of ordinary skill in art could readily recognize identity of a molecule, other than cyclopamine and its salts, suitable for use in the described invention and he/she could obtain further such molecules by methods routinely used in prior art. For example, total chemical synthesis of teratogenic *Veratrum* alkaloids and derivation of these molecules from one another had been described in prior art (see e.g. Kutney JP et al, *Canadian Journal of Chemistry* 1975;53:1796-1817) and a molecule derived from cyclopamine had been used to inhibit Hh/Smo signaling and to obtain the previously known technical effect of the inhibition of cell proliferation (Taipale J et al, *Nature* 2000;406:1005-1009).

In conclusion, numerous naturally occurring and synthetic non-cyclopamine molecules with and without a cyclopamine core were well known in prior art to be suitable for specifically inhibiting Hh/Smo signaling. The specification of the application cites several examples of prior art publications describing such uses of non-cyclopamine molecules. The specification also indicates that molecules can be synthesized so as to possess the disclosed biological effects of cyclopamine (*see e.g.* page 17, lines 22-25). Thus, it is clear to a person skilled in the art that a pharmaceutically acceptable compound that can specifically inhibit Hh/Smo signaling is suitable for use in the described method of treatment. A molecule defined functionally as a molecule that possesses the biological effects of cyclopamine and inhibits Hh/Smo signaling specifically is a clearly defined molecule. The skilled person would have no uncertainty whether a particular non-cyclopamine molecule is within or out of the defined category of molecules. The specification teaches directly that a molecule other than cyclopamine exerting the biological effects of cyclopamine is suitable for use in the described method of treatment. As Dr. Tas explains in ¶¶ 9-10 of his declaration, this functional description is effective to communicate the metes and bounds of the invention, and in fact does so *more effectively* than structural descriptions, attempted in the prior art, were able to communicate the bounds of tetratogenicity between cyclopamine and other compounds.

Given this proven state of the art, which is directly analogous to that of *Unocal* and completely inapposite to that of *Rochester*, the *Unocal* rule applies. As a matter of law, when the skilled person already is familiar with materials having the recited properties "description of the exact chemical component … is not necessary to comply with §112." See *Rochester*, at 69 USPQ2d at 1895.

Written description requirement has been satisfied as to all pending claims. Withdrawal of the Written Description Rejection and allowance of application is requested.

II. Indefiniteness Rejection

Claims 1, 8, 9, 11, 27 and 28 have been rejected under 35 U.S.C. § 112, second paragraph, asserting that the claims fail to particularly point out and distinctly claim the subject matter.

As explained above in relation to the Written Description Rejection, a person skilled in the art would not have difficulty in understanding what the term "derivative" means in the context of the present invention. In particular, there is extensive evidence in the record that a skilled person knows how to identify other compounds that are specific inhibitors of Hedgehog/Smoothened signaling. Withdrawal of the Indefiniteness Rejection and allowance of application is requested.

III. New Claims

Claims 31, 33 and 35 depend respectively from claim 1, 8 and 27 and further explicitly recite that the cyclopamine derivatives are those that specifically inhibit Hedgehog/Smoothened signaling. See Page 3, line 20. This recitation comports with the Examiner's suggested claim group 2). With this recitation, any purported compounds that might conceivably[1] be characterized as cyclopamine derivatives but which do not retain the recited characteristic inhibition property are explicitly excluded by this recitation. Further consideration and allowance of these claims is therefore respectfully requested.

Claims 32, 34 and 36 depend respectively from claim 1, 8 and 27 and further explicitly specify that the medicament comprises cyclopamine or pharmaceutically acceptable salts thereof. This recitation comports with the Examiner's suggested claim group 1) which was indicated to be allowable in the Examiner's interview summary record. Allowance of these claims is therefore respectfully requested.

New independent claims 37, 45, 47 and 50 define treatment methods that recite treatment with "cyclopamine or another compound that specifically inhibits Hedgehog/Smoothened signaling." This recitation is supported by the written description and is understandable to the skilled person for the reasons already discussed. Claims 37 and 45 (like previously presented claims 1 and 27) recite a psoriasis treatment. Claim 47 recites a method of treating "a non-tumoral skin disorder presenting skin lesions." See page 29 lines 11-15; and page 33 lines 9-11 (original claim 2). Claim 50 recites a method of "downregulating epidermal growth factor receptor expression by epidermal cells." See page 28, line 20 - page 29, line 9.

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[1] "Conceivably" in this sentence refers to a hypothetical definition of "derivatives" that improperly ignores the explicit teachings of the present application at page 17 line 20 - page 18, line 16.

Claims 38-40 depend from claim 37 but otherwise are counterparts of claims 8, 9 and 11. Claims 41 and 42 recite that the compound has receptor-binding properties similar to cyclopamine and binds to the same biological target to which cyclopamine binds to inhibit Hedgehog/Smoothened signaling. See page 17, line 22 to page 18, line 6. Claims 43-44 depend from claim 42. Claims 42-44 are otherwise counterparts of claims 8, 9 and 11.

Claim 46 depends from claim 45 but otherwise is a counterpart of claim 28. Claims 48 and 51 depend from respectively from claims 47 and 50, but otherwise are counterparts of claims 32, 34 and 36. Claims 49 and 52 depend respectively from claims 47 and 50, but otherwise are counterparts of claim 41.

The new claims are fully supported by the specification as shown above and hence are also seen to be allowable.

IV. Conclusion

The forgoing amendments and remarks are seen to put the application in condition for allowance. Early and favorable action thereon is requested.

Respectfully submitted,
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